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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/635,949	08/10/2000	Richard A. Shimkets	15966-559 (CURA-59)	5151

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EXAMINER	
ROBINSON, HOPE A	
ART UNIT	PAPER NUMBER
1653	12

DATE MAILED: 05/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/635,949	Applicant(s) SHIMKETS ET AL.	
	Examiner Hope A. Robinson	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *1-4,15-29,31,32 and 34-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *5-14,30 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4, 5* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

1. Applicant's election without traverse of Group II (claims 5-14, 30 and 33, SEQ ID NO:33) in Paper No. 11 is acknowledged.

Specification

2. The specification is objected to because of the following informalities:

The specification is objected to because on page 6, last paragraph reads "Analysis using the PSORT and SignalP computer programs predicted that **there is may** be a signal peptide....." (emphasis added).

Correction is required.

Information Disclosure Statement

3. The information disclosure statement filed on July 2, 2001 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP 609. The items listed on the information disclosure statement are missing from the application; and, a line has been drawn through the following items on the information disclosure statement: B1-B5 and C1-C16.

Claim Objection

4. Claim 5 is objected to because the claim recites non-elected subject matter with respect to the sequences. Note that Paper No. 11 elected SEQ ID NO: 33 without traverse.

Claim Rejections-Utility Rejections Under 35 U.S.C. § 101 And 35 U.S.C. 112, First Paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 5-14, 30 and 33 rejected under 35 U.S.C. 101 because the claimed invention lacks substantial utility.

The claims are directed to nucleic acids encoding proteins that are described as useful as novel members of the protein families according to the presence of domains and sequence relatedness to previously described proteins. However, the disclosure does not identify the protein families that are similar to the claimed protein. In addition, there is no indicia as to the

function assigned to the protein that is suppose to be similar to other protein families. The prior art teaches that "numerous cases exists in which proteins of very different current functions are homologous in that they evolved from a common ancestor and will match with significant sequence similarity. The prior art also teaches that the practice of assigning functions by sequence similarity is dangerous because many of the automatic predictions by most of the software robots are erroneous" (Smith et al., Nature Biotechnology, vol. 15, pages 1222-1223, November 1997) is one of many such references. The claimed polynucleotides are not supported by a substantial asserted utility. Identifying a polynucleotide as encoding a PROX polypeptide does not endow the polynucleotide with such a utility. Identifying a protein as having a limited homology to another family of proteins, which is not known to be a member of a family of similarly acting factors with identifiable functional regions, does not indicate what function it and thus the encoding polynucleotide might have. The specification states that the claimed PROX nucleic and the encoding protein can be used to treat or prevent or delay a PROX-associated disorder in a subject, however, there is no specific disease or specific function that is suggested by this limited homology. The specification indicates that the claimed protein is over expressed in certain tissues thus, the clone has use as a probe. Tissue-specific expression does not rely on specific properties or functions of the encoded protein. Further, the specification does not disclose any diseases or conditions known to be associated with the encoded protein. Note also that the over expression demonstrated in the instant specification is of the nucleic acid which does not unequivocally mean that there will be over expression of the protein. Furthermore, the

specification lists several pages of expression levels in several different tissues which indicates that the probe is not tissue specific. The asserted utility disclosed in the instant specification exemplifies a real world context of use, where further research would be required to identify a disease in which the encoded protein is involved and to identify the families that are homologous and their functions. Additionally the claims are directed to fragments, homologs, analogs and derivatives of the encoded protein, however, there is no indicia what biological activity or attributes the variants of the protein possess. Thus, the polynucleotide lacks substantial utility.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 5-14, 30 and 33 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either substantial asserted utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

7. Claims 5-14, 30 and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification on page 2 states that the invention is based on nucleic acids and secreted polypeptides encoded thereby and fragments, homologs, analogs and derivatives thereof, referred to as PROX and the specification does not provide a definition for "PROX". The specification also states that the methods are provided to treat or prevent or delay a PROX-associated disorder or proliferation-associated disorder in a subject (see page 4). However, no specific disease or disorder is described or exemplified. On page 6 of the disclosure it is stated that PROX nucleic acids and polypeptides are useful as novel members of the protein families according to the presence of domains and sequence relatedness to previously described proteins. However, the specification does not demonstrate or describe any such proteins in association with the claimed invention. The disclosure states that PROX nucleic acids and polypeptides can be used to identify cell types based on the presence or absence of various PROX nucleic acids according to the invention, however, the tables in the disclosure show a broad spectrum of tissue types, thus, specificity is lacking.

On pages 56-57 of the instant specification it is disclosed that Clone 16467945.88 (PROX 17), nucleic acid SEQ ID NO: 33 that encodes polypeptide SEQ ID NO: 34 are highly over expressed in certain breast cancer cell lines, ovarian cancer cell lines, renal cancer cell lines and colon cancer cell lines. Further, the encoded protein is strongly suppressed in lung cancer cell

lines in comparison with normal lung cells. Thus, the disclosure asserts that this clone may be used as a selective probe for detection or diagnosis of these cancers and that the clones or their genes products may be useful therapeutics or target in treatment of such cancers (see also pages 93 and 104 for other asserted use for the protein). The results are said to be presented in Example 16. Example 16 found on pages 150-151 of the instant specification exemplifies Clone 11692010.051 which according to Table 1 found on pages 5-6 represents nucleic acid SEQ ID NO: 5 that encodes polypeptide SEQ ID NO: 6. The disclosure states that the example demonstrates that 11692010 gene product inhibits trypsin at a 50% inhibitory level. It is further stated that proteins exhibiting some similarity to the clone 11692010.051 protein can be potentially used for: 1) the stimulation of growth and motility of keratinocytes; 2) modulation of angiogenesis and tumor vascularisation; 3) the inhibition of the growth of cancer cells (i.e. melanomas); 4) modulation of skin inflammation and 5) modulation of epithelial cell growth. In addition, the protein encoded by Clone 11692020.051 has some degree of similarity to fibromodulin, a protein that potentially regulates extracellular matrix remodeling. Note that the nucleic acid and the encoded protein exemplified in Example 16 is not Clone 16467945.88 (PROX 17), nucleic acid SEQ ID NO: 33 that encodes polypeptide SEQ ID NO: 34. Clone 11692010.051, nucleic acid SEQ ID NO: 5 (2852 nucleotides) that encodes polypeptide SEQ ID NO: 6 (652 residues) is structurally and physically distinct from Clone 16467945.88 (PROX 17), nucleic acid SEQ ID NO: 33 (2112 nucleotides) that encodes polypeptide SEQ ID NO: 34 (584 residues). Thus the statement that proteins exhibiting some similarity to the clone

11692010.051 protein can be potentially used for 1) the stimulation of growth and motility of keratinocytes; 2) modulation of angiogenesis and tumor vascularisation; 3) the inhibition of the growth of cancer cells (i.e. melanomas); 4) modulation of skin inflammation and 5) modulation of epithelial cell growth is not demonstrated in Example 16 as there is no indication of what percent homology to equate with "some similarity" and no examples are provided of Clone 16467945.88 inhibiting trypsin. Based on the variations between the two sequences there is no indication that the same function ascribed to the clone exemplified in Example 16 is retained.

Further, the specification indicates that Clone 11692020.051 has some degree of similarity to the protein fibromodulin and there is no indication of what percent homology to equate with "some degree of similarity". A search of the claimed sequence for Clone 16467945.88 did not produce any results that indicated the sequence is homologous to a protein of the fibromodulin family. Thus, the activity indicated for this protein cannot be assigned to the protein encoded by Clone 16467945.88. Therefore, the instant specification provides no evidence of the asserted function for the encoded protein.

The claims are directed to a nucleic acid and the encoding protein and to fragments, analogs and homologs thereof of the claimed protein, and there is no indicia as to the biological activity of the variants of the protein. In addition, there is no indication as to whether or not the asserted function of the claimed protein is retained in the claimed variants and the claims do not have any functional limitations. Additionally, there is no analogous art.

Further, the claims are directed to a nucleic acid sequence that hybridizes under stringent conditions to the claimed nucleic acid and the specific conditions are not recited in the claims. Note that sequences identified by hybridization, would not predictably have the same structural and functional characteristics as the disclosed species because there is no way to determine what variations would be tolerated. The specification on page 93 indicate that the nucleic acid molecules, proteins, protein homologous and antibodies can be used in the following methods: screening assays, detection assays, predictive medicine, and methods of treatment. However, no standardized screening assay is demonstrated. Additionally, the specification provides no demonstration of specific detection assays or any methods of treatment in association with a specific disease or disorder. It is noted that pages 132+ indicate that Tables 22 and 23 provide primer sequence information and the relative expression results for clones that are highly expressed in central nervous system tumors and melanomas and suppression in colon cancer, breast cancer, ovarian cancer, prostate cancer, lung cancer etc. However, it does not provide evidence of expression of the claimed polypeptide as the expression of the polynucleotides does not unequivocally mean expression of the polypeptides. Typically, when a polynucleotide is expressed in a tissue-specific manner, the polypeptides encoded thereby are also similarly expressed in a tissue-specific manner, one can assume that the polypeptides are expressed in a tissue-specific manner, in the ovary, breast etc. However, absent evidence of this, it is also reasonable to assume that expression of the DNA may not result in expression of the protein.

Note also that pages 133-150 lists all kinds of tissues and expression levels, thus it appears that expression is not tissue specific.

Thus, absent guidance via data as to the use of the encoded protein and a showing of a probe that is specific one of skill in the art would have to engage in undue experimentation to practice the claimed invention. Additionally, undue experimentation would be required to determine if the claimed protein variants are functional or retains the asserted function. Further, no description is provided as to the features or attributes of the claimed variant. There is no indicia as to whether the recited 15% variation in the claimed protein sequence will result in a different protein or one that is not functional. Therefore, the instant specification lacks adequate written description.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 5-14, 30 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 and the dependent claims hereto are indefinite with respect to the variant as the claimed sequence can encompass a variation of 15% and there is no indication as to whether or not the variant will be functional or retain the asserted function of the protein.

Conclusion

9. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Hope A. Robinson whose telephone number is (703)308-6231. The Examiner can normally be reached on Monday - Friday from 9:00 A.M. to 5:30 P.M. (EST).

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor Christopher S.F. Low, can be reached at (703)308-2932.

Any inquiries of a general nature relating to this application should be directed to the Group Receptionist whose telephone number is (703)308-0196.

Papers related to this application may be submitted by facsimile transmission. The official fax phone number for Technology Center 1600 is (703) 308-2742. Please affix the Examiner's name on a cover sheet attached to your communication should you choose to fax

your response. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989).

Hope A. Robinson, MS

Patent Examiner

Christopher S. F. Low

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